

## REMARKS

Claims 45, 46, 49-53, 56-61, 64-68, and 70-72 are pending in this application.<sup>1</sup> Claims 45, 46, 58-61, and 72 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld (U.S. Patent No. 4,016,252; hereinafter “Relyveld”) in combination with Gerhart et al. (U.S. Patent No. 5,085,861; hereinafter “Gerhart”) and Constantz et al. (U.S. Patent No. 5,782,971; hereinafter “Constantz”). Claims 49-53, 56-57, 64-68, and 70-71 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in combination with Gerhart, Constantz, and Classen (U.S. Patent No. 5,723,283; hereinafter “Classen”). By this reply, Applicants amend claims 45, 59, 64, 70, and 72, add new claims 73 and 74, and address each of the Examiner’s rejections.

### Support for the Amendment

Support for the amendment to claims 45 is found in the specification at, e.g., page 10, line 5, through page 11, line 13. Claims 59, 64, 70, and 72 are amended to harmonize the claim language. Support for new claims 73 and 75 is found in, e.g., Examples 19 and 20 on pages 59 and 60 of the specification. No new matter is added by the amendment.

### Rejections under 35 U.S.C. § 103

#### *Relyveld, Gerhart, and Constantz*

Claims 45, 46, 58-61, and 72 stand rejected under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Gerhart, and Constantz. The Office has not supported the obviousness rejection with an articulated reason or a rational underpinning sufficient to support the rejection of claims 45, 46, 58-61, and 72 based on the combination of Relyveld, Gerhart, and

Constantz. For this reason, Applicants respectfully traverse this rejection.

In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the Office to establish a factual basis to support the legal conclusion of obviousness. *In re Fine*, 837 F.2d 1071, 1073 (Fed. Cir. 1988). In so doing, the Office must make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Discussing the question of obviousness of a patent that claims a combination of known elements, the Court in *KSR Int'l v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007), explained:

When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida [v. AG Pro, Inc.*, 425 U.S. 273 (1976)] and *Anderson's-Black Rock[, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969)] are illustrative--a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

*KSR*, 127 S. Ct. at 1740. Although a holding of obviousness can be based on a showing that “there was an apparent reason to combine the known elements in the fashion claimed” (*Id.*, 127 S. Ct., at 1740-41), the *KSR* Court noted that, “[t]o facilitate review, this analysis should be made explicit.” *Id.* at 1741, 82 USPQ2d at 1396 (citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness...[H]owever, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the

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<sup>1</sup> The Office Action Summary omits reference to claim 64, which is currently pending.

art would employ.” *Id.*, 127 S. Ct. at 1741 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

Here, the Office provides no articulated reasoning or rational underpinning sufficient to support its obviousness rejection of claims 45, 46, 58-61, and 72 based on the combination of Relyveld, Gerhart, and Constantz; the Office simply states:

it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the physical characteristics of Reyveld’s [sic: Relyveld’s] composition into an injectable paste, as suggested by Gerhard [sic: Gerhart] and Constantz, and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest” (Office Action, p. 4).

The Office’s conclusion is based solely on the fact that Relyveld, Gerhart, and Constantz describe “calcium phosphate delivery systems that have been shown to be safe and effective” (Office Action, p. 7). The Office’s conclusory statement does not provide a rational basis to combine Relyveld, Gerhart, and Constantz to yield the invention of present claims 45, 46, 58-61, and 72, and thus, it is insufficient to support the Office’s *prima facie* case of obviousness under the Supreme Court’s standards articulated under *Graham* and *KSR*. For the reasons discussed below, the § 103 rejection of claims 45, 46, 58-61, and 72 should be withdrawn.

#### Relyveld Teaches Away from the Invention of Present Claims 45, 46, 58-61, and 72

As was discussed previously (see, e.g., the Reply to Office Action dated November 6, 2006), Relyveld discloses an aqueous gel of calcium phosphate for preparing adsorbed vaccines; the aqueous gel has a solids content two orders of magnitude less than the vaccine delivery composition of present independent claims 45, 59, and 60, and claims dependent therefrom (see, e.g., the Abstract). Relyveld states:

it is highly desirable that the particles of the suspension be as fine as possible. This requirement is well met by the gel of the present invention, which exhibits a marked colloidal character. The fineness of particles in the gel of the invention is demonstrated by the fact that the velocity of settling of the gel is much slower than that of conventional calcium phosphate gel. (Col. 2, lines 2-9; emphasis added.)

Relyveld clearly discloses a calcium phosphate gel that should be administered as a fine, particulate *suspension*; this disclosure directly teaches away from the cement compositions of Gerhart and Constantz because it directs skilled artisans away from the preparation of a hardenable, injectable paste having a solids content of greater than or equal to 40 wt%, as is recited in present claims 45-54 and 56-72.

The M.P.E.P. § 2144.05(III) states that “[a] *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)” (emphasis added). *See also KSR International Co. v. Teleflex Inc.*, 82 U.S.P.Q.2d (BNA) 1385, 127 S. Ct. 1727, 1739-40 (2007) (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious). A reference teaches away when a skilled artisan, upon reading the reference, would be led on a divergent path from the one taken by the Applicants. Although “any need or problem known in the field of endeavor at the time of invention and addressed by the [present application] can provide a reason for combining the elements in the manner claimed” (see *KSR*, 127 S. Ct. at 1742), it is necessary for the Office to establish a sufficient basis for concluding that one skilled in the art would combine the reference teachings to yield the claimed invention. *See In re Icon Health and Fitness, Inc.*, 83 U.S.P.Q.2d (BNA) 1746, 496 F.3d 1374, 1381 (Fed. Cir. 2007).

Here, Relyveld fails to teach or suggest substantially increasing the solids content of the

aqueous gel composition beyond that of about 3.3 wt %, and certainly not greater than or equal to 40 wt%, as is recited in present claims 45, 46, 58-61, and 72, and, in fact, teaches the opposite: an aqueous gel suspension of fine particulates. Thus, Relyveld directly teaches away from a vaccine delivery composition formulated as a hardenable, injectable paste with a high solids content, such as the vaccine delivery composition of present claims 45-46, 58-61, and 72.

The Office cites Gerhart and Constantz to remedy the deficiencies of Relyveld, yet fails to provide a rational explanation for why one of skill in the art would modify the composition of Relyveld according to Gerhart and Constantz. Gerhart and Constantz do not describe or suggest the preparation of vaccine compositions, nor do they describe or suggest that calcium phosphate containing gel formulations should be reformulated as pastes. Instead, Gerhart describes a “biodegradable cement composition adapted for use in the surgical repair of living bone and for the controlled release of pharmaceutical agents” (Gerhart, col. 4, lines 19-22), while Constantz states:

calcium phosphate cements may be used for a variety of purposes, such as any form of connective tissue replacement, including bone cement, an injected prosthetic implant, a prosthetic orthopaedic or dental implant, as a root canal filler, a prophylactic injection to augment weak osteoporotic bone, to fill voids resulting from fracture reduction, or a vehicle for drug delivery. (Constantz, col. 6, lines 56-62.)

Both Gerhart and Constantz disclose that their cement compositions can be used as drug delivery vehicles, but neither teaches or suggests that the cement compositions can or should be used as an immunological vaccine delivery composition, which the art teaches to contain only small amounts of fine calcium phosphate particles in suspension (see Relyveld and Classen, discussed below). The only reason provided by the Office in support of its combination of Relyveld with Gerhart and Constantz is that each of these publications describes compositions

that include calcium phosphate, which is a “safe and effective delivery system” (Office Action, p. 7). This simple conclusion by the Office ignores the fact that the Relyveld composition is formulated for a completely different purpose (i.e., vaccination) than that of the Gerhart and Constantz compositions (i.e., a bone cement and bone cement/drug delivery composition, respectively) and that Relyveld explicitly guides the skilled artisan in the direction of a vaccine composition having a dilute suspension of fine calcium phosphate particles, rather than in the direction of a vaccine composition that is formulated as a hardenable, injectable paste having greater than 40 wt% calcium phosphate. The fact that calcium phosphate, as a component of a composition, can be safely administered does not provide any motivation to alter the characteristics of Relyveld’s dilute aqueous suspension, which Relyveld states is the desired formulation, to be more like that of the Gerhart and Constantz compositions. The Office’s statement is a bare assertion without support.

Gerhart and Constantz simply fail to provide any teaching or suggestion to combine their reference teachings with that of Relyveld to yield the invention of present claims 45-46, 58-61, and 72. Moreover, a skilled artisan would not modify Relyveld’s aqueous gel suspension according to the teachings of Gerhart and Constantz in light of Relyveld’s explicit preference for a fine particulate suspension, which is the opposite result achieved by Gerhart and Constantz. The mere fact that these publications can be combined or modified does not render the resultant combination obvious unless the prior art publications also suggest the desirability of the combination, which, in this case, they do not (*In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) quoting *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); “The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.”). Other than a

conclusory statement, the Office has articulated no reason that supports a legal conclusion of obviousness against present claims 45, 46, 58-61, and 72, nor has the Office addressed the fact that Relyveld directs skilled artisans away from the formulations disclosed by Gerhart and Constantz. For these reasons, the Office has not met its burden of establishing a *prima facie* case of obviousness against present claims 45, 46, 58-61, and 72. This rejection should be withdrawn.

*Relyveld, Gerhart, Constantz, and Classen*

Claims 49-53, 56-57, 64-68, and 70-71 stand rejected under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Gerhart, Constantz, and Classen. The Office states:

Classen is used to provide general knowledge in the art of vaccine formulations. Classen teaches the use of various cytokines in combination with an immunogenic agent to enhance the clinical response...It would have been obvious to one of ordinary skill in the art at the time of invention to employ a cytokine or immunogenic adjuvant, as described by Classen, because addition of either or both cytokines and secondary adjuvants would have increased the specificity, the duration of exposure and further improved the induction of an immune response. (Office Action, pp. 5 and 6).

Applicants respectfully traverse this rejection.

Relyveld, Gerhart, and Constantz are discussed *supra*. As is acknowledged by the Office, Classen provides only general knowledge in the art of vaccine formulations. Classen, like Relyveld, only describes a dilute vaccine composition. Classen states:

Vaccines are diluted using sterile technique in sterile phosphate buffer solution pH 7.4 using the notation 1:100 to indicate 1 part vaccine per 100 part PBS by volume. Vaccines were administered by intraperitoneal injections for convenience though other routes would be effective. (Col. 35, lines 34-38.)

Thus, both Classen and Relyveld teach away from a vaccine delivery composition that is

formulated as a hardenable, injectable paste having a solids content of greater than or equal to 40 wt%. For this reason, both Classen and Relyveld fail to provide the skilled artisan with any reason to combine their reference teachings with those of Gerhart and Constantz to yield the vaccine delivery composition of present claims 49-54, 56-57, and 64-72. Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 49-54, 56-57, and 64-72 for obviousness over Relyveld in combination with Gerhart, Constantz, and Classen be withdrawn.

CONCLUSION

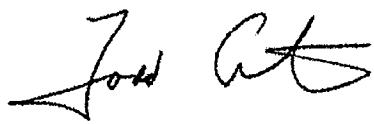
In view of the above remarks, Applicants respectfully submit that the pending claims are in condition for allowance, and a notice to that effect is respectfully requested.

A petition to extend the period for replying to the Office Action for three months, to and including January 12, 2009, as January 11, 2009, fell on a Sunday, is submitted herewith.

Applicants authorize the Office to deduct the fee required by 37 C.F.R. § 1.17(a) for the petition from Deposit Account No. 03-2095.

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,



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